IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: DIGITEK® PRODUCT LIABILITY LITIGATION **MDL NO. 1968**

THIS DOCUMENT RELATES TO ALL CASES

DEFENDANTS' GENERAL BACKGROUND STATEMENT OF KEY FACTUAL INFORMATION REGARDING DIGITEK

While recognizing that this Court is generally familiar with many of the key facts in this litigation, Defendants believe it will be helpful to the Court to have many of those facts collected in one place with appropriate record references as it considers the many motions being filed, including:

1. Defendants' Motion for Summary Judgment (all MDL cases);
2. *Daubert* challenges to the PSC's four general liability product defect experts (all MDL cases);
3. A Motion for Summary Judgment in *Vega* based on *Daubert* challenges;
4. A Motion for Summary Judgment in *McCornack* based on *Daubert* challenges; and
5. Motion in Limine to Exclude Unreliable Hearsay (all MDL cases).

I. THE DRUG DIGOXIN

Digitek® is a pharmaceutical tablet product designed to deliver the active pharmaceutical ingredient ("a.p.i.") digoxin. Digoxin is a plant-based pharmaceutical that has been used for hundreds of years. It falls into the family of cardiac glycosides, and is generally used to treat two diseases—an arrhythmia called atrial fibrillation, and congestive heart failure. (Reports of

Walter Kernan, M.D., Defendant's General Liability Expert, Ex. 1, and Marc Semigran, M.D., Plaintiffs' General Liability Expert, Ex. 2. A list of exhibits is attached hereto.)

It is widely known and undisputed that digoxin products have a "narrow therapeutic window," meaning there is a fine line between a therapeutic dose of the medication and a dose that might be toxic to the patient. (Ex. 3, Semigran Dep. at 37.) Because digoxin has such a narrow therapeutic range, the mere fact that a patient exhibits an elevated blood level or experiences digoxin toxicity cannot support an inference that the patient received too much of the drug, whether in the form of too many tablets or tablets that contained too much digoxin. (*See,* generally, testimony of Mark Semigran, M.D., and report of Walter Kernan, M.D.). As Plaintiffs' general causation experts acknowledge, there are a variety of reasons other than excess dose why a patient taking digoxin could exhibit either an elevated digoxin blood level or symptoms of digoxin toxicity. (Ex. 3 at 37, 51, 59-61, 100-101; Ex. 4, Nelson Dep. at 59, 67-68, 70, 55, 57, 141.) Even taking a double dose of digoxin does not automatically mean a patient will become toxic, or be harmed, because patients and their reactions are variable. (Ex. 3 at 114-155; Ex. 4 at 93, 95.) And far more often than not, digoxin toxicity is not fatal; its manifestations are usually transient. (Ex. 5, Delgado Dep. at 367; Ex. 3 at 64-66.) Even at appropriate dose levels digoxin has serious risks, including death. (Ex. 4 at 51.)

II. ACTAVIS PRODUCING AND SELLING DIGITEK®.

Digitek® tablets were first marketed in the early 1990s by Actavis Totowa's predecessor company, Amide Pharmaceuticals. Amide produced Digitek® until 2005, when Actavis Totowa took over following an acquisition and continued production until April, 2008. All Digitek® manufactured by Amide and Actavis after 1999 was sold to Mylan and Mylan either distributed the Digitek® or sold it to its subsidiary UDL Labs for distribution. (*See* Ex. 6.)

III. THE DIGITEK® RECALL

In the spring of 2008, the FDA inspected Actavis Totowa regarding the proposed transfer of certain functions from one facility (Little Falls, NJ) to another (Riverview, NJ). During the inspection the FDA examined numerous aspects of the production including the report for a manufacturing defect investigation that occurred in the context of manufacturing Digitek® batch 70924A, which was manufactured between November 17 and 20, 2007. This batch investigation led to the all-lots recall of Digitek®. (*See* Ex.7, Actavis Defendants Answers to Plaintiffs First Set of Interrogatories, # 9; *see* also Ex. 8.)

On November 30, 2007, in the course of packaging batch 70924A, a line operator found two tablets that appeared to be twice their appropriate thickness. The packaging operators promptly shut down the line and inspected several buckets of tablets, finding one additional too-large tablet. They resumed the packaging operation, but found two more double-thick tablets in the last bucket. Shortly thereafter, Actavis's Quality Assurance and Manufacturing departments met, discussed the batch, and placed it on "hold" until a more thorough investigation could be completed. (Ex. 9.)

Between January 15 and 18, 2008 Actavis unpackaged all of batch 70924A and conducted a visual inspection of every tablet. This inspection unearthed 15 more double-thick tablets—resulting in a final total of 20, out of just under 4.8 million in the batch. Then, on January 22, the Company conducted an additional, tightened sampling inspection, randomly testing 40 tablets from each of 33 full buckets, and 10 from a partial 34th bucket. No further double-thick tablets were found. Ultimately, the batch was repackaged and released for distribution on January 28, 2008. It was sent to Mylan shortly thereafter. (Ex. 9.)

When the FDA learned about the circumstances of the investigation into batch 70924A, the FDA inspector on site suggested a recall. Initially, the FDA only requested that Actavis

recall batch 70924A. (Ex. 10.) On April 24, 2008, however, Actavis and the FDA agreed to a recall of all batches of Digitek® that were on the market and within their expiration dates.[1] (Ex. 11.)

The April 25, 2008 Digitek® recall press release, which received FDA approval, reported that "[t]he voluntary all lot recall is due to the possibility that tablets with double the appropriate thickness may have been commercially released." (Ex. 12) (emphasis added). The downstream notices sent to pharmacy customers said the same thing, and the recall package, also an FDA-approved document, said: "Digoxin tablets exceeded tablet thickness specifications." (Ex. 13.) In short, the recall at all times focused only on the possibility that double-thick tablets were released to the market. The notices do not say there was, in fact, defective product sent to market, and do not even say defective product probably was sent to market. (Ex. 14, Bliesner Dep. at 72-73; 104.)

The FDA confirmed that its concern was double-thick tablets—and indicated its view that the recall did not pose a significant public health threat—in a 2009 statement posted on its website. (Ex. 8.) The statement, part of a document titled "Facts and Myths about Generic Drugs," reported that:

> In March 2008, FDA performed a scheduled inspection of the Actavis production facility and identified products that were not manufactured to required specification over a period of time extending back to the year 2006. Included in this list of products was one particular lot of Digitek.

[1] Actavis recalled 171 batches. *See* Ex. 7, Actavis Defendants' Answers to Plaintiffs' Second Set of Interrogatories, # 40. Of those, 152 batches had actually been distributed beyond Mylan or UDL to pharmacies. *Id.* (indicating 153 batches were distributed to market; however, after Defendants responded to the interrogatories, they learned that one of the 153 batches listed in information they had submitted to the FDA, which formed the basis for their response to this interrogatory, was listed twice, meaning the actual number of distributed batches was 152). The approximate total number of recalled tablets (both dose strengths) was 680 million, manufactured beginning in early 2006. *Id.*

> Actavis detected a very small number of oversized tablets in this lot (specifically, 20 double-sized tablets in a sample of approximately 4.8 million tablets).
>
> Although Actavis attempted to remove the affected Digitek tablets through visual inspection, FDA determined that this method of removal was inadequate to assure the product's quality and consistency in accordance with the current Good Manufacturing Practice (cGMP) regulations.
>
> Since the detection of the manufacturing problem, FDA has been actively engaged with this company to ensure that **ALL** potentially affected lots of Digitek tablets have been recalled. In our best judgment, given the very small number of defective tablets that may have reached the market and the lack of reported adverse events before the recall, harm to patients was very unlikely. (Emphasis added.)

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last visited July 7, 2011) (emphasis added).[2]

The recall—as this statement confirms—did not result from or in any way relate to any alleged defect other than potentially double thick tablets, such as (as Plaintiffs more recently argue) normal-sized tablets containing too much or too little digoxin, or any formulation change and/or manufacturing error affecting bioavailability.

The distinction between oversized tablets and tablets of normal size but containing too much active pharmaceutical ingredient is factually and legally significant. Oversized tablets and normal sized tablets with too much a.p.i. are different pharmaceutical manufacturing problems, and the FDA knows the difference. (*See*, e.g., testimony of Plaintiffs' four pharmaceutical experts Somma (Ex. 15 at 191-193), Kenny (Ex. 16 at 119-124), Farley (Ex. 17 at 425-427), and Bliesner (Ex. 14 at 68-71, 73). And, precautionary recalls are undoubtedly conducted, even

[2] Defendants request that this Court take judicial notice of the FDA's statement. The content of a government agency's position articulated on its website is a fact "capable of accurate and ready determination by resort to resources whose accuracy cannot reasonably be questioned.": Fed. R. Evid. 201(b)(2). "Information generated through a government agency's web site falls within Fed. R. Evid. 201(b)(2), and courts have routinely considered such information to be self-authenticating for purposes of Fed. R. Evid. 902(5)." *Brackett v. Corinthian Mort. Corp.*, 2010 WL 1254705, at *2 (Bkrty. N.D. W.Va. Mar. 25, 2010).

when there is no proof that distributed products are, in fact, outside specifications, or even likely to be. (Ex. 16 at 43-44; Ex. 15 at 23-25; Ex. 17 at 365-367; Ex. 14 at 82-84.)

IV. NO DEFECTIVE TABLETS HAVE BEEN IDENTIFIED DURING DISCOVERY

There are several different types of defect that could occur while making tablets. These include: too thin, too thick (with or without too much active ingredient), too much active ingredient, or too little active ingredient. The focus in the litigation by Plaintiffs has been on too thick or too much active ingredient.

Rule 26 (a)(2) and (a)(3) of the FRCP regarding disclosures would require any MDL plaintiff – or the PSC as a representative body – to identify test results showing either a "double thick tablet," or a normal size tablet with too much a.p.i. (or, theoretically, any other defect). In addition, Plaintiff Fact Sheets ("PFS"), filled out by every plaintiff and claimant, ask for any testing information, as do interrogatories in the remaining cases. Aside from Rule 26 and discovery documents, simple self interest would motivate the PSC to identify tested, defective Digitek®. As of August 1, 2011, more than three years after the recall, the PSC has never identified even one defective Digitek® tablet in the hands of their clients.

V. THE FDA APPROVED EVERY ASPECT OF THE DIGITEK® MANUFACTURING PROCESS.

Before a generic pharmaceutical company receives FDA approval to market a drug, it must submit and receive approval of an Abbreviated New Drug Application ("ANDA"). Amide's ANDA was approved on December 23, 1999. (Ex. 18.) The ANDA must be supported by data showing the company has the proper equipment and methods to consistently make the drug within its specifications.

Every aspect of pharmaceutical manufacturing—including the equipment and the step-by-step process used to manufacture a drug—must be "validated" by the company and approved

by the FDA. Process validation involves repeated manufacturing and dose testing to assure every step of the process works correctly and is capable of being repeated, every time, and to assure that a product can be consistently manufactured to its FDA-approved specifications. (Ex. 15 at 78; Ex. 14 at 45, 553; Ex. 17 at 344.) The overall Digitek® manufacturing system was validated and a "Process Validation Report" was executed and submitted to the FDA in December 1994. The process was validated again multiple times after 1994 as the Company increased its batch sizes. (*See* Ex. 19, 20, 21, 22, 23.) Thus, all of Actavis's processes for Digitek® were validated. (Ex. 15 at 60-61; Ex. 14 at 46) Once validated, these processes need not be re-validated, and here they remained validated through 2008. (Ex. 15 at 60-62, 92; Ex. 16 at 79-80.) FDA did not cite or warn Actavis about validation issues. (Ex. 14 at 142-144.)

Companies like Actavis weigh, count, and/or test their product at every stage of the manufacturing process and maintain extensive "batch" records for each step as part of an exhaustive effort to ensure that product is produced according to specification and that the validated process remains "in control." These company records offer direct proof that Digitek® was consistently made within specifications. An FDA-approved specification, formula, or regulation governs every step of the manufacturing process, including:

- **The Formula –** The FDA approves the formula for blending Digitek® and there are FDA-approved specifications for weighing, counting, and measuring the amount of raw materials used in the manufacturing process.

- **The Blending Process** – FDA-approved specifications govern the process for blending together ingredients. The FDA approves the equipment used and also approves quality-control measures, such as the methods for reconciling the amount of ingredient used against the formula, and for the weighing and chemical testing of samples to assure "blend uniformity."

- **The Tableting Process** – The FDA approves the process for converting blend material into tablet form, approves the equipment used, and also approves quality-control steps such as inspecting tablets for thickness, weight, appearance, and hardness, and for weighing and counting of final product to reconcile with the amount of raw ingredient used.

- **The Packaging Operation** – The FDA approves the equipment and the process used in the packaging operation, in which Digitek® tablets are placed in containers that are, in turn, counted and weighed again to reconcile against the amount of materials used.

- **Affirmative Product Testing**—The FDA requires chemical testing of finished tablets to ensure they meet their specifications for active pharmaceutical ingredient (assay testing) and contain a consistent dose from tablet to tablet (content uniformity testing).

If a pharmaceutical company put too much a.p.i. into batches of digoxin there are many opportunities during and after the manufacturing process to detect out-of-specification finished product. (Ex. 15 at 107-108; Ex. 14 at 93; Ex. 16 at 142, 146-149.) For example, it could be detected in inventory patterns, blend tests, finished product testing, outside testing, or adverse event reporting. None of those occurred here.

If the tablets are too thick, there are also a number of stages after leaving Actavis at which they could be detected: repackaging (i.e. UDL), FDA inspections, pharmacists, consumers, or their lawyers. (Ex. 15 at 185; Ex. 17 at 436-437.) None of those occurred in connection with any recalled Digitek®.

If Actavis had mass produced Digitek with too much digoxin, two things could have been reasonably expected to happen: first, there would have been outbreaks of toxicity in the United States; second, adverse event reporting to FDA would have increased. But neither happened. Each expert witness for Plaintiffs either denies finding a spike in toxicity nationwide, or even in their own hospital, or never looked. (Ex. 4 at 54; Ex. 3 at 23; 117; Ex. 17 at 368; Ex. 5 at 235.) The FDA specifically noted no increase in adverse event reports before the recall (Ex. 8) and was not critical of Actavis's AER reporting in this period. The PSC has no expert evidence otherwise.[3] (*See* Ex. 24, report of Stan Music.)

[3] The PSC withdrew their pharmacovigilance expert, Karen Frank. She offered no opinions about whether there was defective Digitek® distributed to consumers.

VI. AFFIRMATIVE PRODUCT TESTING CONFIRMS ACTAVIS CONSISTENTLY PRODUCED WITHIN-SPECIFICATION DIGITEK®.

Two sets of direct evidence demonstrate that the FDA-approved Digitek® manufacturing process remained at all relevant times "in control," and that Actavis consistently produced within-specification tablets: First, company records showing that Digitek® tablets consistently tested within specification; and second, records from third-party testing (including testing by the FDA itself) that corroborate the company records.

A. Actavis's Own Testing

It is axiomatic that pharmaceutical manufacturers cannot test 100% of their product; there would be nothing left to sell. (Ex. 15 at 56-57; Ex. 17 at 118-119; Ex. 16 at 47.) Therefore, they develop sampling plans which the FDA must approve. (Ex. 15 at 57-58; Ex. 17 at 253.) There is no claim that Actavis's FDA-approved sampling plans were substandard. (Ex. 15 at 59-60, 63-66, 114; Ex. 16 at 115-117.)

Actavis has produced detailed production records for each of the 152 recalled batches, which total over 680 million tablets. Each of the 152 recalled batches was tested by Actavis at each stage described earlier, using FDA-approved test methods and sample sizes. Each batch met Digitek® specifications. (Ex. 15. at 104, 114; Ex. 17 at 417; Ex. 14 at 53-54, 141-142, 566.) These produced records constitute direct, documented proof that the validated processes for making Digitek® remained in control.[4] (*See* reports of defense experts Bennett (Ex. 25), Snee (Ex. 26), Kaiser (Ex. 27), Amsel (Ex. 28) and Hilscher (Ex. 29).)

[4] There is no claim, at least in the PSC's experts' reports or depositions, that these documents are falsified or unreliable. (*See* Ex. 15 at 66-67, 114; Ex. 17 at 105-108; Ex. 16 at 60, 190)

B. Outside Testing

There is also substantial, direct, pre-litigation evidence from outside Actavis that Digitek® in the market was within specifications. In fact, all testing evidence – including outside testing – showed Digitek® that was in the market was within its specifications. (Ex. 15 at 165, 240; Ex. 17 at 393, 417; Ex. 14 at 53-54, 141-142, 566.)

1. FDA Testing

The FDA's "batch certification" program in the 1990s provided for pre-release analysis of pharmaceutical batches by the FDA. In a June 1995 letter, the FDA certified 9 Amide-manufactured Digitek® batches. (Ex. 30.) So satisfied was FDA with Amide's compliance regarding Digitek® that by July 1995 the FDA exempted Digitek® from further batch certification requirements. (Ex. 31.) This means Actavis was reliably following its validated methods. (Ex. 14 at 47-48.)

Digitek® continued to pass FDA scrutiny after 1995 as part of the FDA's ongoing surveillance program routinely undertaken for drugs with a narrow therapeutic window. From time to time the FDA would remove a sample of Digitek® from the company, a distributor, or a pharmacy, test the sample, and then issue a Form 484 report. All of these documents were available either in this litigation from Actavis or from FDA via a FOIA request.

Between 2002 and 2008, the FDA collected at least 11 samples of Digitek® pursuant to the 484 program: four in 2002, two in 2007, and five in 2008. The FDA, using United States Pharmacopeia ("USP") test methods, subjected each sample to assay, content uniformity, and dissolution testing. Every sample, each from a different batch over that time frame, tested within specification. (*See* Ex. 32-42.) Seven of the samples the FDA tested, all from 2007 and 2008, were ultimately among the 152 recalled batches, meaning, the FDA independently tested

samples from 4.6% of the recalled batches using the USP method and, in doing so, corroborated Actavis's own quality control test results.

Most of Plaintiffs' experts never reviewed this evidence before their depositions; one expert (Bliesner) looked at it only the day before his deposition. None of them, however, dispute any of these facts or the test results. (*See*, generally Ex. 17 at 399; Ex. 15 at 121-136; Ex. 14 at 106-108, 111-113, 118; Ex. 16 at 69-77, 84-92, 94-100.)

2. UDL/Mylan Testing

Mylan, who distributed Digitek® manufactured by Actavis, sold a portion of the Digitek® bought from Actavis to one of its subsidiaries, UDL. UDL received the Digitek® in bulk bottles and repackaged it into single-dose units, commonly called "blister packs." A double-thick tablet would not fit in UDL's blister packs. UDL makes its blister packs to accommodate Digitek® tablets with, at most, a thickness of only up to 110% of Actavis's maximum tablet thickness. (*See* Ex. 43.) "Double thick" tablets would be far too large to fit in a blister pack – the blister cavity would be damaged and the packaging equipment would shut down. (Ex. 44, Radtke Dep. at 137; 140-141.) In addition, UDL subjected each batch of Digitek® it received to random sampling for thickness. (Ex. 44 at 50, Ex. 43.) UDL never found any tablets that were too-thick or not thick enough, much less any double-thick tablets. (Ex. 43.)

UDL, as a repackager, also did stability testing on the contents of the tablets in some batches, including assay and dissolution testing. This testing, performed on 34 Digitek® batches, by independent laboratories hired by Mylan and UDL, corroborates Actavis's own quality control testing and assured that the batches met potency specifications. (*See* Ex. 45-52.) Actavis recalled 11 of these 34 batches, meaning 7.2% of the recalled batches were subjected to chemical testing for potency; all tablets met appropriate specifications.

When combined with the testing performed as part of FDA's 484 program, this data establishes that 11.8% (18 of 152) of recalled Digitek® batches were tested for potency, in accordance with USP procedures, by outside laboratories. The number of batches tested is statistically significant and is direct evidence that the Digitek® in the market was not defective Digitek®. (*See* report of defense expert Ron Snee (Ex. 26). Mr. Snee is the only statistical expert identified in the MDL cases.)

The PSC's experts do not dispute the results of this testing. (*See* Ex. 17 at 401-405; Ex. 15 at 142-156; Ex. 14 at 125-127, 128-139; Ex. 16 at 104-110.)

3. Quantic Regulatory Services

Another independent analysis confirms the quality of Digitek®. The January 9, 2007 FDA warning letter to Actavis (amended February 1, 2007) requested that Actavis retain a third party to audit its records regarding various drug products, including Digitek®. (Ex. 53.) To comply, Actavis hired Quantic Regulatory Services – a hire that was approved by the FDA. Quantic has an excellent reputation, and several of the PSC's experts have worked with Quantic. (Ex. 17 at 267, 385-386; Ex. 14 at 183-186, 191-192.) Quantic examined a wide variety of data, including lab notebooks, calculations and approval procedures, raw material data, release documents, equipment usage logs, manufacturing batch records, in-process analyses, and yield calculations. Quantic completed its audit by December 21, 2007, and Actavis communicated Quantic's results to the FDA on December 24, 2007. The results reflected evaluation of 39 Digitek batches (among other drugs), and indicated that manufacturing and laboratory records reliably confirmed the identity, strength, quality, and purity of Actavis's products. (Ex. 54, Bates ACTAV001867195, 001867199 and 001867209.) Of these 39 Digitek® batches, 19 were recalled; thus, an additional 19 batches of recalled Digitek® were subjected to independent record review by an FDA-approved auditor, and that review indicates Actavis's records reflect

manufacturing of within-specification Digitek®. Plaintiffs' experts have no reason to disagree with what Quantic found. (Ex. 16 at 61-63, 68, 152-153; Ex. 17 at 387; Ex. 15 at 119-120; Ex. 14 at 185-188.)

In short, abundant direct evidence, specific to Digitek®, reveals a process in control, producing a drug within its specifications. Plaintiffs have no direct evidence to the contrary.

VII. THE REGULATORY HISTORY OF DIGITEK

Unable to produce direct evidence of defective Digitek®, either through physical observation or scientific testing, Plaintiffs focus on Actavis's relationship with the FDA. There, Plaintiffs find (as they would with any pharmaceutical manufacturer) documents related to Actavis's manufacturing of all its drug products, including Digitek®. Some of these documents allege regulatory violations and Plaintiffs hope to present them as evidence of defective Digitek®, even though they have nothing to do with whether (and do not state that) Digitek® tablets contained too much or too little digoxin. To understand why this evidence cannot satisfy Plaintiffs' burden to prove defect, a basic understanding of how the FDA regulates drug manufacturing is essential. For a thorough discussion of the difference between regulatory findings and true product failures, see *United States v. Barr Labs., Inc.,* 812 F. Supp. 458 (D. N.J. 1993).

A. FDA manufacturing process regulation.

The primary mechanism through which the FDA regulates the drug manufacturing process is set forth in 21 C.F.R. §§ 210 and 211, which constitute the current Good Manufacturing Practice Regulations ("cGMPs") applied to pharmaceuticals. The cGMP regulations impose a wide variety of requirements, regulating everything from personnel qualifications (21 C.F.R. § 211.25), to labeling operations (21 C.F.R. § 211.130), to laboratory

testing for release and distribution (21 C.F.R. § 211.165). As one court has explained, cGMP provisions are "prophylactic measures" designed "to *prevent* the distribution of poorly manufactured drugs and devices 'by giving the Food and Drug Administration . . . additional authority to require that sound methods, facilities, and controls be used in all phases of drug manufacturing and distribution." *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1285 (D. P.R. 1992). Simply, "the GMP regulations are intended to be preventive." *Id.*

Like other FDA-enforced preventative regulations, cGMPs are policed through regulatory action only, not civil suits. *See* 21 C.F.R. § 210.1(b) ("[S]uch drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action."). That is, only the FDA can punish a manufacturer for violating a cGMP provision; there is no private right of action through which consumers can sue a manufacturer for violating cGMPs (or any provision of the FDCA). *See, e.g.*, *PhotoMedex, Inc. v. Irwin*, 601 F.3d 919, 924 (9th Cir. 2010); *Alpharma, Inc. v. Pennfield Oil Co.*, 411 F.3d 934, 939 (8th Cir. 2005).

B. <u>How a drug becomes "adulterated" under the FDCA.</u>

Anytime a manufacturing process falls short of a cGMP requirement, the resulting product is deemed "adulterated":

> A drug or device shall be deemed to be adulterated . . . .[I]f it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administrated in conformity with current good manufacturing practice . . . .

21 U.S.C. § 351(a)(2)(B). Applying this definition, whether a drug is "adulterated" or not has nothing to do with whether the final product met its content specifications and/or whether it is safe for consumption. Everything turns on whether the manufacturing *process* satisfied the

FDA's regulations. A drug product will be rendered "adulterated" if *any* aspect of the manufacturing process did not fully comply with any cGMP.

The meaning of adulteration, and what can be inferred from it, is not at issue in this litigation. The FDA's website states:

> If a company is not complying with cGMP regulations, any drug it makes is considered "adulterated" under the law. This kind of adulteration means that the drug was not manufactured under conditions that comply with cGMP. It does not mean that there is necessarily something wrong with the drug.
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> * * * * *
>
> The impact of cGMP violations depends on the nature of those violations and on the specific drugs involved. A drug manufactured in violation of cGMP may still meet its labeled specifications, and the risk that the drug is unsafe or ineffective could be minimal.

(Ex. 55) (emphasis added).[5] The PSC's experts admit this statement is true - adulteration does not equate to defect or "outside specification." (Ex. 15 at 74-76; Ex. 17 at 83, 101, 195-196, 409-411, 413-414, 416; Ex. 14 at 27-28, 31, 85-86; Ex. 16 at 51, 55, 76, 229.)

Under the FDCA, therefore, a finding of "adulteration" (an allegation Plaintiffs have pressed throughout this litigation) means at most that the drug was manufactured in a way that violated a cGMP regulation, regardless of what that regulation requires. To determine *how* a drug is adulterated, and whether the manufacturing problem is of the kind that could harm a consumer, it is necessary to dig deeper and investigate what the cGMP provision at issue required. For example, a pharmaceutically perfect drug could be manufactured, sealed, and packaged, and yet *still* be rendered "adulterated" because the labeling on the drug bottle is upside-down. *See* 21 C.F.R. § 211.125 ("Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production

[5] Defendants request that this Court take judicial notice of this FDA's statement. *See* n. 2 *supra*.

records."). The PSC's experts will not identify any cGMP violations which go specifically to Digitek® production or drug dose in general.

C. FDA documents produced in discovery.

In this litigation, Plaintiffs have consistently featured documents alleging Actavis produced "adulterated" Digitek®, including inspection reports and letters issued by the FDA. These documents take a variety of forms, but a basic understanding of what they are helps to clarify their significance and role in the regulatory context:

> Establishment Inspection Reports – An "Establishment Inspection Report," commonly referred to as an "EIR" is a "narrative report stating what occurred and what was undertaken during an FDA inspection." *United States v. John D. Copanos & Sons, Inc.*, 831 F.2d 466, 468 (4th Cir. 1987). An EIR not only describes what the FDA agent inspected, but also what the inspector observed in terms of compliance (or noncompliance) with the FDA's cGMP regulations. EIRs reflect the observations set forth on the 483 for the same inspection and also contain additional, fact-based comments of the FDA investigator. They are not typically immediately made available to the manufacturer, and they are not used to notify manufacturers of conditions the FDA investigator believes reflect a cGMP deficiency. An EIR is less formal than a warning letter. (Regulatory Procedures Manual at 10-2-4, Ex. 56.)
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> Form 483s – A Form 483 is the first formal notice that a manufacturer receives from the FDA with regard to alleged cGMP deficiencies. The form is a "Notice of Inspectional Observations," issued by the FDA's field investigator, and contains a list of any conditions the FDA inspector believes deviates from the cGMP regulations as observed by the investigator. Paul W. Goebel, Matthew D. Whalen, & Felix Khin-Maung-Gyi, *What A Form 483 Really Means*, Applied Clinical Trials Online, Sept. 1, 2001, http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=92055 (last visited May 17, 2011).
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> A 483 is the *opinion* of the FDA investigator on the scene; it is not an official FDA position. *Id.* Rather, the list of alleged cGMP violations is a way to begin a formal dialogue with the manufacturer's representative about ways to correct manufacturing process problems. *See In re Abbott Laboratories Derivative Shareholders Litigation*, 325 F.3d 795, 799 (7th Cir. 2003) ("After each inspection, the FDA first sends a Form 483 to the manufacturer which notes any deviations under the CGMP, then discusses the findings with the manufacturer's representative, and requests a plan for correcting the violations."). A 483 is also less formal than a WL (Regulatory Procedures Manual at 10-2-4, Ex. 56.)

> Warning Letters – Warning letters are more significant than Form 483s in that they communicate the FDA agency position on alleged cGMP violations, as opposed to just the observations of the field investigator. A warning letter is an "informal and advisory" method by which the FDA "communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action." Regulatory Procedures Manual (March 2010) (Ex. 57 at 4-2, *available at* http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf (last visited May 17, 2011)).
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> Warning letters, the FDA explains, issue "only for violations of regulatory significance," but are *not* final agency action. *Id.* Instead, the FDA's goal in sending a warning letter is to persuade the manufacturer to voluntarily "correct violations of the statutes or regulations." *Id.*

Plaintiffs build their case here – and intend to try to prove product defect – almost entirely using these kinds of documents.

The key regulatory issues Plaintiffs believe are relevant to this litigation involve 483s and Warning Letters issued to Actavis as a result of inspections that occurred between 2006 and 2008. These include:

1. **2006 #1** – Pharmacovigilance Inspection 1/10-2/8/06 (483 2/8/06; WL 8/15/06) (*See* Ex. 58 and Ex. 59).

2. **2006 #2** – Inspection (Little Falls) 7/10-8/10/06 (483 8/10/06; WL 1/9/07, revised 2/1/07) (*See* Ex. 60, 61 and 62).

3. **2006 #3** – Inspection (Taft Road) 9/18-10/11/06 (483 10/11/06) (*See* Ex. 63).

4. **2006 #4** – Inspection (Taft Road) 10/24-25/06 (*See* Ex. 64).

5. **2007** – Inspection 9/5-28/07 (Little Falls); (483 9/28/07) (*See* Ex. 65).

6. **2008** – Inspection 3/18-5/20/08 (Riverview and Little Falls); (483 5/20/08) (*See* Ex. 66).

Of the FDA regulatory documents relating to these six inspections, only three contain any reference at all to Digitek®.

The FDA's observations specifically about Digitek® amounted to:

1. 2/8/06 – Digitek® AER reporting issues (referring entirely to events which occurred in 2003 or earlier) (Ex. 58, 59);[6]

2. 8/10/06 – cleaning validation testing method not verified under all uses (Ex. 61 at 4; Ex. 62 at 4-5);

3. 5/20/08 – product failing to meet specifications and quality control criteria "are not rejected," referring to batch 70924A, the batch which triggered the recall. (*See* p. 2-3, infra); issue with the way manufacturing investigation was conducted when the Company encountered blend uniformity test issues on three batches (one of the three batches was rejected by quality control because of "atypical content uniformity results.").

The AER reporting issues identified in the August 2006 FDA Warning Letter which resulted from the inspection that ended February 8, 2006 were corrected successfully to the express satisfaction of the FDA, and did not refer to events near the recall period. (Ex. 72; Ex. 14 at 528.) Likewise, the cGMP cleaning validation issue involving Digitek®, that is set forth in the August 2006 FDA 483 and February 2007 revised Warning Letter, also was corrected to the complete satisfaction of the FDA. (*See* 9/28/07 EIR, Ex. 68 at 30-31; Ex. 61 at 4; Ex. 62 at 4-5.) Indeed, all GMP deficiencies identified in the 2006 FDA inspection were completely corrected by the time of the September 2007 FDA inspection according to the FDA. (Ex. 68 at 25-38.)

With respect to blend uniformity testing, the ingredients are gathered and then blended in a dry powder blend using large equipment. When the blending is done, an FDA-approved sampling program dictates how to take small core samples from ten different blender locations, with backup samples, which are tested to see if the active ingredient digoxin is uniformly spread throughout the batch. (Ex. 14 at 531.) The process can be a challenge, and can have human sampling and/or analytical errors. (Ex. 14 at 199 200; Ex. 16 at 171.) If a sample is off, an investigation is conducted into the reason for the out-of-specification result. In certain

[6] Again, the Plaintiffs have withdrawn the only expert who was hired to talk about adverse event reporting and pharmacovigilance. The defense expert in these issues, Stan Music, stands unrebutted.

circumstances, testing the backup sample(s), which is/are taken at the same time and from the same location as the primary sample, is an acceptable and FDA-approved method – conducting testing of back-up samples in appropriate circumstances is expressly written into the FDA-approved Company SOPs which describe how to conduct blend uniformity testing. (Ex. 14 at 202-203; 530, 532; Ex. 16 at 170-171.) If testing the backup sample is permitted, and if the test result for the backup is within specification, the batch can be compressed and ultimately released, assuming it passes all required content uniformity testing conducted on in-process samples taken during compression of the batch. (Ex. 14 at 533, 535-536.) If not, depending on the investigation and more testing, circumstances may dictate that the batch be rejected. (Ex. 14 at 204-205, 532.)

As the FDA 483 for the 2008 inspection clearly indicates, the FDA never cited or warned Actavis for blend uniformity failures, or for releasing batches with blend uniformity issues where unevenly blended batches should have been rejected. The criticism by the FDA was that the Company did not conduct adequate investigations into the initial out-of-specification blend uniformity test results before testing the backup sample – the FDA form 483 citations related to the technical aspects of investigating out–of-specification core samples, and did not relate to true blend failures. (Ex. 66 at 6; Ex. 14 at 200, 204-207; Ex. 15 at 97, 99, 100-101, 105-106.) Mr. Kenny had no opinion about the blend issue. (Ex. 16 at 213.)

Except for the FDA criticizing the Company's decision to not reject the single batch (#70924A) where some defectively thick tablets were discovered during production (but were removed entirely before distribution and never made it to market), the only FDA criticisms applicable to Digitek® related to things which are not at issue in this litigation – adverse event reporting, cleaning validation testing failures (neither of which say anything about the final

content of the drug), and the method the Company used to investigate circumstances where an initial out-of-specification result was obtained when conducting blend uniformity testing on three batches of Digitek®.

VIII. ONE VERIFIED INSTANCE OF OUT-OF-SPECIFICATION DIGITEK® IN THE MARKET

The Plaintiffs' experts' opinions rely in great degree on the one and only known instance of an extra thick tablet in the market, which happened years before the events at issue in this litigation. In 2004 a pharmacist found one extra thick Digitek® tablet. It was returned to Actavis, a manufacturing investigation was conducted, and the situation was reported to FDA. (Ex. 69-70.) After reviewing the Actavis investigation, FDA said:

> No additional complaints or reports of thick tablets have been received for this high volume product. The event was considered an isolated incident and corrective actions were put in place to prevent its reoccurrence. Corrective actions (procedural enhancements and review of complaint files) were verified during the inspection.

(Ex. 71 at 6.) This is the *only* verified report of a too-thick Digitek® tablet leaving Actavis's facilities. The tablet was produced in 2003; all recalled Digitek® was produced in 2006 or later.

Since 2003 well over one billion Digitek® tablets have been made and distributed to the marketplace. This single 2003-produced tablet is the only Digitek® tablet in the marketplace found to be out of specification for any attribute.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on August 1, 2011, a copy of the foregoing was filed electronically. Notice of this filing will be sent to all parties by operation of the Court's electronic filing system. Parties may access this filing through the Court's system.

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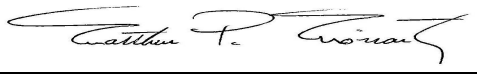
By: 

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DEFENDANTS' GENERAL BACKGROUND STATEMENT OF KEY FACTUAL INFORMATION REGARDING DIGITEK

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2	Marc J. Semigran, M.D. Expert Report
3	Marc J. Semigran, M.D. Deposition 6/23/10
4	Eljorn D. Nelson, Pharm. D. Deposition 6/22/10
5	Reynolds M. Delgado III, M.D. Deposition 10/19/09 (pages 1- 196) and 5/25/11 (pages 197-393)
6	Supply & Distribution Agreement
7	Answers of Defendants Actavis Inc., Actavis Totowa LLC and Actavis Elizabeth LLC to Plaintiffs' First Set of Interrogatories Directed to Defendants and Defendants Actavis Totowa LLC, Actavis Inc., and Actavis Elizabeth LLC's Responses to Plaintiffs' Second Set of Interrogatories
8	7-9-09 FDA website statement
9	Investigation Deviation Report
10	4-23-08 e-mail re FDA requested recall
11	E-mail FDA all lots of Digitek to be recalled
12	Recall Press Release
13	The Recall Package
14	David Bliesner, Ph.D. Deposition 1/25/11 (pages 1-242) and 2/18/11 (pages 243-581)
15	Russell Somma, Ph.D. Deposition 7/1/10
16	Mark G. Kenny Deposition 6/29/10 (pages 1-300) and 2/16/11 (pages 301-580)
17	James J. Farley Deposition 6/28/10 (pages 1- 326) and 1/19/11 (pages 327-459)
18	12-23-99 ANDA Approval Letter
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26	Ronald D. Snee, Ph.D. Expert Report
27	Jeffrey M. Kaiser Expert Report
28	Lewis P. Amsel, Ph.D. Expert Report
29	Sean W. Hilscher Expert Report
30	6/95 batch certification letter
31	7/95 FDA exemption letter
32	FDA Form 484 2/9/07 Sample #377410
33	FDA Form 484 12/18/07 Sample #448881
34	FDA Form 484 12/18/07 Sample #448892

EXHIBIT NO.	EXHIBIT DESCRIPTION
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66	FDA Form 483 5/20/08 70924 and blend uniformity
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